REMARKS

Examiner Interview

The Applicants thank Examiner Lukton for the helpful comments and suggestions made during the November 6, 2003 telephone interview that was kindly granted. During that discussion, issues raised in the office action and claim amendments as reflected in this response were discussed.

Status of Claims

Claims 22-63 are pending. Claims 1-21 are cancelled. Claims 32, 36, 38, 44, 45 and 51-53 are withdrawn from further consideration. Claims 22-31, 33-35, 37, 39-43, 46-50 and 54-63 are rejected.

By this amendment, claims 22, 32, 36, 38, 41, 42, 44, 45, 51-55, 57, 59 and 61 have been amended, without prejudice or disclaimer of any previously cancelled subject matter. Claims 64-98 have been added. Upon entry of this amendment, claims 22-98 will be pending. Support for the claim amendments are found in the specification, *e.g.*, from page 4, line 9 to page 15, line 7, as described in more detail below. No new matter has been added.

New Claims

New independent claim 64 is similar to independent claim 22 and recites a valency platform molecule "comprising a moiety of the formula $-OCH_2CH_2O-$." Support for this claim limitation is found throughout the specification, for example, on page 4, lines 30-34; page 9, line 31 to page 10, line 10; page 12, lines 12-21; and page 20, lines 4-9. Dependent claims 65-97 correspond to currently pending depending claims 23-63. New claim 98 depends from claim 22 and recites a valency platform molecule comprising a moiety of the formula $-OCH_2CH_2O-$. Support for this claim limitation is as stated above.

Claim Amendments

Claim 22

Claim 22 has been amended to incorporate a limitation wherein the valency platform molecule "has a single line of symmetry." Support for this amendment is found throughout the specification, as detailed below.

For example, Formulas 1 and 2 on page 4, lines 15-25, depict valency platform molecules suitable for use within the invention. These formulas are reproduced below:

$G^{[1]} \{T^{[1]}\}_{n[1]}$ Formula 1

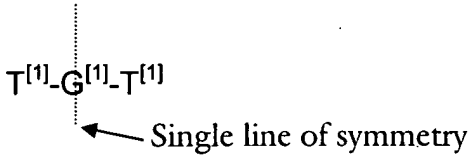
$G^{[2]} \{L^{[2]} - J^{[2]} - Z^{[2]} (T^{[2]})_{p[2]}\}_{n[2]}$ Formula 2

Page 6, lines 28-35 list values for $n^{[1]}$ and $n^{[2]}$, which include $n^{[1]} = 2$ and $n^{[2]} = 2$. When $n^{[1]} = 2$ and $n^{[2]} = 2$, Formulas 1 and 2 may be represented by modified Formulas 1 and 2 (Formulas 1m and 2m) shown below:

$T^{[1]}\text{-}G^{[1]}\text{-}T^{[1]}$ Formula 1m

$_{p[2]}(T^{[2]})\text{-}Z^{[2]}\text{-}J^{[2]}\text{-}L^{[2]}\text{-}G^{[2]}\text{-}L^{[2]} - J^{[2]} - Z^{[2]} (T^{[2]})_{p[2]}$ Formula 2m

It is further stated on page 6, lines 1-5, that in one embodiment, all of the $n^{[1]}$ moieties shown as $T^{[1]}$ are identical. The resulting valency platform molecule has a single line of symmetry, as shown below:



Similarly, Formula 2m provides a valency platform molecule having a single line of symmetry when the variables on either side of $G^{[2]}$ are identical. The specification fully encompasses and supports such compounds. Page 6, lines 2-5 state that all of the $p^{[2]}$ moieties shown as $T^{[2]}$ may be identical. It is further stated on page 7, lines 11-12 that all of the $n^{[2]}$ moieties shown as $Z^{[2]}$ may be identical. Taking these disclosures together, Formula 2m may be depicted as shown below, wherein the bold type indicates independently identical groups.

$$(\mathbf{T^{[2]}})_{p2}\text{-}\mathbf{Z^{[2]}}\text{-}\mathbf{J^{[2]}}\text{-}L^{[2]}\text{-}G^{[2]}\text{-}L^{[2]}\text{-}\mathbf{J^{[2]}}\text{-}\mathbf{Z^{[2]}}\text{-}(\mathbf{T^{[2]}})_{p2}$$

The above depicted valency platform molecule contains a single line of symmetry when both of the $L^{[2]}$ moieties are identical and both of the $J^{[2]}$ moieties are identical.

$L^{[2]}$ and $J^{[2]}$ are defined on page 6, lines 24-27. Therein, $L^{[2]}$ is limited to O, NR^{sub}, or S. $J^{[2]}$ is limited to C(=O) or C(=S). Hence, there are only a few number of chemical moieties from which $L^{[2]}$ and $J^{[2]}$ may be chosen. In addition, throughout the specification and examples, $L^{[2]}$ and $J^{[2]}$ are independently identical. For example, in Figure 6A, compounds 3-I and 3-II, both of the $L^{[2]}$ moieties are O and both of the $J^{[2]}$ moieties are C(=O). The same is true for compounds 20-I, 20-II, 20-III and 20-IV in Figure 6B, as well as the compound shown in Figure 7.

Both $L^{[2]}$ and $J^{[2]}$ encompass a narrowly defined set of chemical moieties and the Applicants disclose numerous examples wherein the $L^{[2]}$ and $J^{[2]}$ moieties are independently identical. The valency platform molecules thus provided have a single line of symmetry, as shown below.

$$(\mathbf{T^{[2]}})_{p2}\text{-}\mathbf{Z^{[2]}}\text{-}\mathbf{J^{[2]}}\text{-}L^{[2]}\text{-}G^{[2]}\text{-}L^{[2]}\text{-}\mathbf{J^{[2]}}\text{-}\mathbf{Z^{[2]}}\text{-}(\mathbf{T^{[2]}})_{p2}$$

Single line of symmetry

Further support for the limitation directed to the valency platform molecule having a single line of symmetry may be found in reference to valency platform molecules depicted in Formulas 6 and 7 on page 12, lines 1-10 of the specification. These formulas are reproduced below:

$G^{[6]}\{O - C(=O) - NR^{SUB} - Q^{[6]} (T^{[6]})_{p[6]}\}_{n[6]}$ Formula 6

$G^{[7]}\{O - C(=O) - N(Q^{[7]} (T^{[7]})_{p[7]/2})_2\}_{n[7]}$ Formula 7

Page 13, lines 19-21 state that in one embodiment, all of the $n^{[6]}$ x $p^{[6]}$ moieties shown as $T^{[6]}$ and all of the $n^{[7]}$ x $p^{[7]}$ moieties shown as $T^{[7]}$ are identical. Page 4, lines 23-26 further state that all of the $n^{[6]}$ moieties shown as $Q^{[6]}$ may be identical and that all of the $n^{[7]}$ moieties shown as $Q^{[7]}$ may be identical. Page 14, lines 1-4 state that $n^{[6]}$ may equal 2 and page 14, lines 9-11 state that $n^{[7]}$ may equal 2. Taken together, the above disclosure supports valency platform molecules having a single line of symmetry as shown in modified Formulas 6 and 7 below.

$(T^{[6]})_{p6}\ Q^{[6]} - R^{SUB}N - (O=)C - O - G^{[6]} - O - C(=O) - NR^{SUB} - Q^{[6]}\ (T^{[6]})_{p6}$ Formula 6m

Single line of symmetry

$((T^{[7]})\ Q^{[7]})_{p[7]/2}N - (O=)C\text{-}O\text{-}G^{[7]}\text{-}O - C(=O) - N(Q^{[7]}\ (T^{[7]}))_{p[7]/2}$ Formula 7m

Single line of symmetry

Further support for the limitation directed to a valency platform molecule having a single line of symmetry may be found throughout the examples in the specification as filed, such as the following valency platform molecules: compound 3, page 31; compound 11, page 32; compound 17, page 33; compound 20, page 34; compounds 30a and 30b, page 37; compound 33, page 38; and compounds 41 and 42, page 39.

Claim 22 has also been amended to recite a valency platform molecule "wherein the valency of said platform molecule is four or more." Support for this amendment is described on, *e.g.*, page 6, line 7 to page 7, line 5 and on page 14, lines 1-14.

Claim 22 has also been amended to recite a valency platform molecule comprising branching groups, wherein the number of branching groups pre-determines the number of attachment sites for biologically active molecules. This amendment streamlines the claim. Conjugation of biologically active molecules to the valency platform molecule in the present

invention takes place via attachment sites located on the valency platform molecule as described, *e.g.*, in the Modes for Carrying Out the Invention section of the specification, starting on page 17. The number of attachment sites that are present on the valency platform molecule corresponds to the valency of the valency platform molecule.[1]

Withdrawn claims

Withdrawn claims 32, 36, 38, 44, 45, 51, 52 and 53 have been amended to reflect new dependencies.

Claims 41 and 42

Claims 41 and 42 have been amended to state "a moiety" of the formula listed.

Claims 54, 55, 57, 59 and 61

Claims 54, 55, 57, 59 and 61 have been amended to recite linking moieties attached to the valency platform molecule. Support for this amendment may be found, for example, on page 22, lines 29-34 and on page 28, lines 19-26.

No new matter has been introduced by the new or amended claims.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Applicants request rejoinder of appropriate method claims to the extent that they incorporate all limitations of allowed composition claims. Applicants further note an election of species in this case. Applicants respectfully traverse the withdrawal of claims 36, 38, and 51-53 and request their rejoinder on grounds given by the office.

[1] Valency is independent of actual occupancy, as it denotes only an upper limit, and not an actual occupancy.

Applicants are submitting a supplemental information disclosure statement concurrently with this amendment.

Rejection under the Judicially Created Doctrine of Obviousness-type Double Patenting

Applicants present arguments with respect to these rejections below. Applicants will address any remaining issues upon obtaining otherwise allowable subject matter.

U.S. Patent No. 5,276,013

Claims 22 and 26-31 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 5,276,013. Applicants respectfully traverse the rejection. Claim 1 of U.S. Patent No. 5,276,013 recites a conjugate of a biologically stable valency platform molecule and a multiplicity of polynucleotide duplexes. However, claim 1 of U.S. Patent No. 5,276,013 does not teach or suggest the specific structural characteristics of the valency platform molecule that are claimed in claim 22 and 26-31 of the instant application. In particular, there is no suggestion in claim 1 of U.S. Patent No. 5,276,013 of a valency platform molecule comprising branching groups, wherein the valency is predetermined by the number of branching groups. In addition, there is no suggestion in claim 1 of U.S. Patent No. 5,276,013 for valency platform molecules having a single line of symmetry, as recited in amended claim 22.[2] The specific structural characteristics recited in claim 22 and dependent claims 26-31 render these claims patentably distinct from claim 1 of U.S. Patent No. 5,276,013. Applicants note the disclosure on the top of columns 17 and 18 in U.S. Patent No. 5,276,013. Applicants respectfully request withdrawal of the rejection.

U.S. Patent No. 6,060,056

Claim 22 is rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 6,060,056. Applicants

respectfully traverse the rejection. Claim 1 of U.S. Patent No. 6,060,056 recites a conjugate comprising a nonimmunogenic valency platform molecule. However, claim 22 of the instant application claims a conjugate comprising a valency platform molecule with specific structural features, such as branching groups, wherein the number of branching groups predetermines the valency of the platform molecule. In addition, claim 1 of U.S. Patent No. 6,060,056 does not suggest a valency platform molecule having a single line of symmetry, as amended claim 22 recites. These limitations are not obvious in view of the broad recitation of a "nonimmunogenic valency platform molecule" in claim 1 of U.S. Patent No. 6,060,056. Applicants assert that claim 22 in the present application is patentably distinct from claim 1 of U.S. Patent No. 6,060,056. Applicants note the disclosure in, *e.g.*, Figure 11 of U.S. Patent No. 6,060,056. Applicants respectfully request withdrawal of the rejection.

U.S. Patent No. 5,552,391

Claim 22 is rejected under judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 5,552,391. In response, Applicants respectfully traverse the rejection and will address any remaining issues upon obtaining otherwise allowable subject matter.

U.S. Patent No. 5,276,013

Claim 22 is rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 9 of U.S. Patent No. 5,276,013. Applicants respectfully traverse the rejection. Claim 9 of U.S. Patent No. 5,276,013 depends from claim 2, which in turn depends from claim 1. Claim 1 of U.S. Patent No. 5,276,013 is discussed above. Claim 2 requires that the valency platform molecule be a polymer and claim 9 further requires that the biologically active molecule be a polynucleotide. However, the further limitations of claim 2 and claim 9 in U.S. Patent No. 5,276,013 do not cure the deficiencies of claim 1. Specifically, claim 9 of U.S. Patent No. 5,276,013 does not teach or suggest the valency platform molecules with the

[2] Applicants' position with respect to this issue is not predicated on these additional amendments. This applies to all obviousness-type double patenting rejections.

claimed structural features, including branching groups wherein the number of branching groups predetermines the valency of the valency platform molecules. Further, claim 9 of U.S. Patent No. 5,276,013 does not suggest valency platform molecules having a single line of symmetry, as the amended claim recites. As such, claim 22 of the instant application is patentably distinct over claim 9 of U.S. Patent No. 5,276,013. Applicants note the disclosure on the top of columns 17 and 18 in U.S. Patent No. 5,276,013. Applicants respectfully request withdrawal of the rejection.

U.S. Serial No. 08/769,041

Claim 22 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 2 of U.S. Serial No. 08/769,041. U.S. Serial No. 08/769,041 has been abandoned, rendering this rejection moot. Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 22-31, 33-35, 37, 39-43, 46-50, 54-63 and 26-31 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection. Applicants note, *e.g.*, page 3, lines 9-30 and page 19, lines 14-19 of the specification. The valency of the claimed valency platform molecules is predetermined by the number of branching groups added to the platform molecule. This relationship requires the presence of a branching group to have a positive correlation to the number of attachment sites on the valency platform molecule. As such, a branching group gives rise to attachment sites for biologically active molecules. Thus, the number of branching groups predetermines the valency *and location* of attachment sites for biologically active molecules. However, in order to expedite prosecution, and without conceding the correctness of the rejection, Applicants have amended claim 22 to recite a limitation wherein the number of branching groups pre-determines the number of attachment sites for biologically active molecules.

Rejections under 35 U.S.C. §102(e)

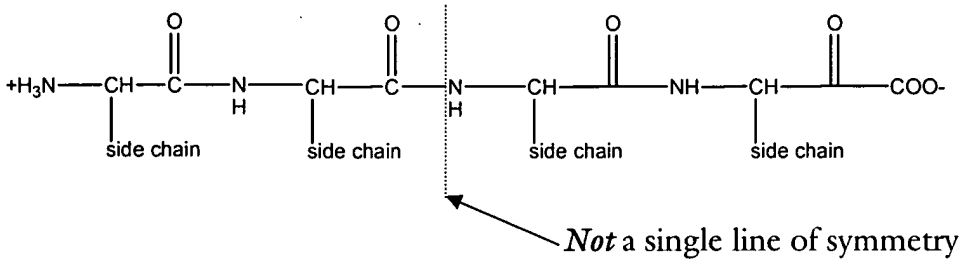
U.S. Patent No. 5,747,244

Claims 22-24, 26, 29, 30, 58-62 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Sheridan in U.S. Patent No. 5,747,244 ("the '244 patent"). Applicants respectfully traverse the rejection. The Examiner states that the '244 patent discloses compositions which contain a peptide to which oligonucleotides are covalently bonded via a linker. The Examiner further states that preferred peptides contain lysine and that lysine itself is "branched". Applicants note that the '244 patent is directed to nucleic acid probes immobilized on a polystyrene surface. The nucleic acid probes may be an oligonucleotide bound to a peptide, as stated by the Examiner.

The three component system disclosed in the '244 patent does not teach or suggest conjugates as recited in claim 22 or the dependent claims thereof. Linkage of a peptide and an oligonucleotide does not teach the limitations recited in claim 22. In particular, neither a peptide nor an oligonucleotide teaches the limitation of a valency platform molecule wherein the valency is predetermined by the number of branching groups. A peptide of amino acid monomer units does not teach a platform with branching groups wherein *the number of branching groups predetermines the valency.* The amino acid monomer units of a peptide are distinguished by their different side chains. Each amino acid unit necessarily comprises a side chain, but not all amino acid side chains in a peptide are available for binding to a biologically active molecule. For instance, if the side chain of lysine is to be considered a branching group by the Examiner, then each and every amino acid side chain should be considered a branching group, whether it be the side chain of phenylalanine, serine, proline, or any other amino acid. However, not all amino acid side chains are available for binding to a biologically active molecule. As such, the carbon that gives rise to an appended side chain in a polypeptide is not a branching group wherein the number of branching groups pre-determines the number of attachment sites for biologically active molecules. Even if the peptides disclosed in this reference would be considered to have branching groups giving rise to the side chains, binding of a substance, such as an oligonucleotide, to a peptide to form a conjugate is not due to the *number* of branching groups (which have side chains) on a peptide, but rather, is solely a function of the specific chemical reactivity and availability of a particular side chain.

Accordingly, the number of side chains present in a peptide does not predetermine the valency. As such, this rejection may be properly withdrawn.

Applicants note that claim 22 has been amended to recite a single line of symmetry. A peptide does not have a single line of symmetry. Peptides have a core chain of amide bonds which link one amino acid monomer to the next. A consequence of repeating amide linkages is that the resulting structure, irrespective of the side chain moieties, precludes the presence of a single line of symmetry, as shown below.



Likewise, an oligonucleotide comprised of nucleic acid monomer units does not teach a platform wherein the number of branching groups predetermines the valency of the platform molecule. As further detailed below, an oligonucleotide does not comprise branching groups wherein the number of branching groups predetermines the valency. In addition, Applicants note that claim 22 has been amended to recite a single line of symmetry. An oligonucleotide does not have a single line of symmetry. Hence, neither a polypeptide nor an oligonucleotide teaches the valency platform molecule claimed in claim 22 or the dependent claims thereof.

In summary, the '244 patent does not teach a conjugate comprising a valency platform molecule having branching groups wherein the number of branching groups predetermines the valency of the valency platform molecule. Further, the '244 patent does not teach a conjugate comprising a valency platform molecule having a single line of symmetry, as recited in amended claim 22. The dependent claims under the same rejection, such as claim 62 which recites trivalent functionalized branching moieties, are not taught by the '244 patent. As such, Applicants assert that claim 22 and the dependent claims thereof are not anticipated by the '244 patent and respectfully request withdrawal of the rejection.

U.S. Patent No. 5,278,051

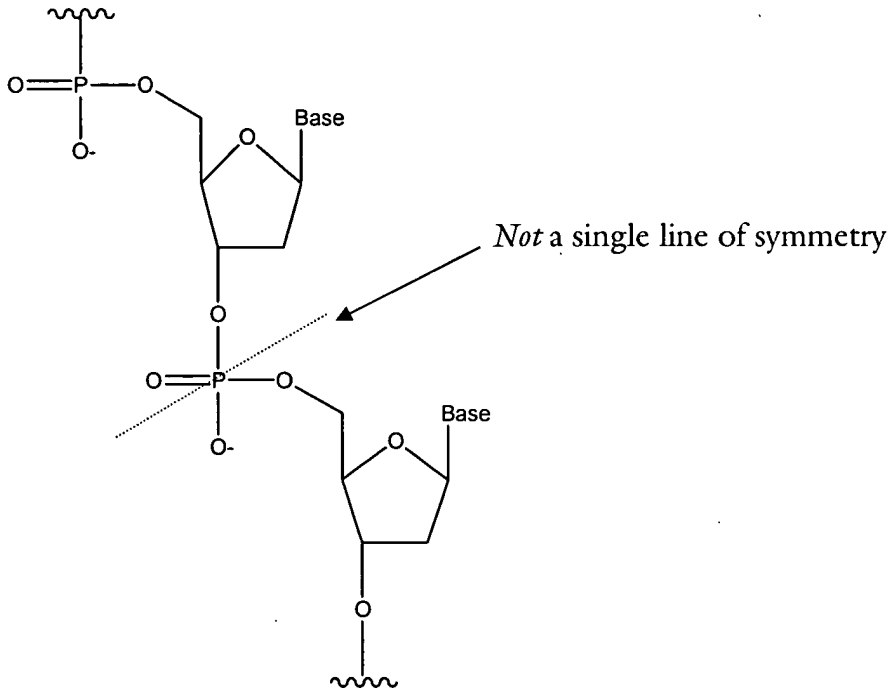
Claims 22, 26, 27, 29, 30, 58-61 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Seeman in U.S. Patent No. 5,278,051 ("the '051 patent"). Applicants respectfully traverse the rejection. The '051 patent discloses various structures that have been prepared from polynucleotides. The Examiner notes that the term "valency platform molecule" in the present claims does not preclude polynucleotides and that both the valency platform molecule and the biologically active molecules may be a polynucleotide. Applicants respectfully disagree. Although the biologically active molecules of the conjugates claimed in the present application may well be polynucleotides, the claim limitations with respect to the valency platform molecule exclude polynucleotides from acting as or teaching valency platform molecules as claimed. Namely, a polynucleotide does not comprise branching groups wherein the valency is predetermined by the number of branching groups. That is, even if nucleic acid monomer units were to be considered to have branching groups, the valency of a polynucleotide is not predetermined by the number of branching groups.

The Examiner uses Figures 2 and 7 of the '051 patent as examples of conjugates between a "first" polynucleotide and a "second" polynucleotide. In this way, the phosphodiester linkage of a nucleotide is considered a branch off of the furan ring of the nucleic acid monomer, and the polynucleotide to which it is linked is considered a biologically active molecule. Applicants respectfully disagree and assert that a phophodiester linkage is not a branching group as claimed.

Further, polynucleotides are comprised of nucleic acid monomer units, wherein each monomer unit contains a base moiety and a phosphodiester linkage from one nucleic acid monomer to the next. In this sense, the structure of polynucleotides is similar to that of polypeptides, wherein each monomer contains a side chain and an amide linkage from one amino acid to the next. However, if the side chain of an amino acid monomer is to be considered a branching group by the Examiner, the base appendages of a nucleic acid would also be considered a branching group. However, according to the teachings of this reference, the base components of nucleic acid monomers do not result in attachment sites for biologically active molecules. Consequently, the polynucleotides do not comprise branching groups according to the present claims, wherein the

number of branching groups predetermines the valency of the valency platform molecule. As such, this rejection may be properly withdrawn.

Additionally, polynucleotides do not comprise a single line of symmetry which is a claim limitation in amended claim 22. Irrespective of any given base moiety, the polynucleotide backbone of phosphodiester linkages precludes the presence of a single line of symmetry, as shown below:



In this section of the Office Action, the Examiner states that the term at issue (valency platform molecule) encompasses any molecule with branch points, such that formation of conjugates is facilitated. However, Applicants assert that the claims at issue require more than just a branch point. Specifically, the claims require the valency platform molecule to comprise branching groups wherein the number of branching groups predetermines the valency of the valency platform molecule. The '051 patent does not teach this limitation. In addition, amended claim 22 requires that a valency platform molecule has single line of symmetry. The '051 patent does not teach the limitations of amended claim 22.

The limitations recited in claim 22 and the dependent claims thereof require specific structural features that are not taught in the '051 patent. Applicants respectfully request withdrawal of the rejection.

U.S. Patent No. 5,386,020

Claims 22, 26, 27, 29, 30, 58-61 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Seeman in U.S. Patent No. 5,386,020 ("the '020 patent"). The '020 patent discloses branched polynucleotide molecules. In the Office Action, the Examiner asserts that a branched polynucleotide qualifies as a conjugate between a polynucleotide valency platform molecule and a polynucleotide biologically active molecule and further states that there is nothing in the specification to exclude the possibility that a valency platform molecule can be a polynucleotide. Applicants respectfully traverse the rejection.

Applicants refer the Examiner to the statements above regarding polynucleotides.

Further, Applicants assert that the claims exclude the possibility that a polynucleotide be considered a valency platform molecule or teach the valency platform molecules claimed. Polynucleotides do not comprise branching groups wherein the number of branching groups predetermines the valency or number of attachment sites for biologically active molecules. Even if the phosphodiester and base appendages of a polynucleotide were to be considered branching groups, no direct relationship exists between the number of branching groups and the valency. In contrast, the instant claims require that the number of branching groups pre-determine the valency of the valency platform molecules. This rejection may be properly withdrawn.

Further, claim 22 has been amended to recite a valency platform having a single line of symmetry. As discussed above, polynucleotides do not comprise a single line of symmetry. Polynucleotides cannot have a single line of symmetry by virtue of the phosphodiester linkages from one nucleic acid to the next. The '020 patent does not teach the claimed invention and Applicants respectfully request withdrawal of the rejection.

U.S. Patent No. 5,527,524 and U.S. Patent No. 6,177,414

Claims 22-24, 33-35, 54, 56, 59-63 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Tomalia in U.S. Patent No. 5,527,524 ("the '524 patent") or Tomalia in U.S. Patent No. 6,177,414 ("the '414 patent"). Applicants respectfully traverse the rejection. Both the '524 patent and the '414 patent disclose "polymer conjugate materials comprising dense star polymers or STARBURST™ polymers associated with desired materials" (column 1, lines 35-39 of '524 patent and column 1 lines 36-38 of the '414 patent). Column 1, lines 54-58 of the '524 patent states that "STARBURST™ polymers exhibit molecular architecture characterized by regular dendritic branching with radial symmetry. These radially symmetrical molecules are referred to as possessing "STARBURST™ topology". Column 1, lines 53-56 of the '414 patent recite the same. This topology is achieved by the ordered assembly of organic repeating units in concentric, dendritic tiers around an initiator core (column 1, lines 60-62 of the '524 patent; column 1, lines 59-61 of the '414 patent). It is further stated in both patents (column 2, line 62 to column 3, line 1 of the ''524 patent and, column 2, lines 53-59 of the '414 patent) that the STARBURST™ dendrimers are unimolecular assemblages possessing three distinguishing architectural features: an initiator core, interior layers radially attached to the initiator core, and an exterior surface of terminal functionality.[3]

The STARBURST™ dendrimers have radially attached interior units and radial symmetry. As well known in the chemical arts, a compound possessing radial symmetry may be cut through the center into equal parts along two or more lines. A compound with radial symmetry thus has multiple lines of symmetry.

Without conceding the correctness of the rejection, claim 22 has been amended to recite that the valency platform molecule has a single line of symmetry. Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §103

U.S. Patent No. 4,933,288

U.S. Patent No. 5,130,116

[3] Applicants note the disclosure of organic amines as the core compound, *e.g.*, ethylenediamine which produces a tetra-branched dendrimer as stated in column 4, lines 24-28 of the '414 patent and column 4, lines 61-65 of the '524 patent.

U.S. Patent No. 4,808,705

U.S. Patent No. 4,981,979

Claims 22-25, 33, 35-37, and 44 are rejected under 35 U.S.C. §103 as allegedly unpatentable over Greenfield in U.S. Patent No. 4,933,288 ("the '288 patent") or Woo in U.S. Patent No. 5,130,116 ("the '116 patent") or Ferris in U.S. Patent No. 4,808,705 ("the '705 patent") or Sivam in U.S. Patent No. 4,981,979 ("the '979 patent"). Applicants address the teachings of each of the '288, the '116, the '705, and the '979 patents immediately below. The Examiner's comments made in this section of the Office Action are addressed thereafter.

The '288, '166, '705, and '979 patents each teach immunoconjugates. The '288 patent discloses expression vectors for the production and processing of proteins that are heterologous to the host cell. The '288 patent thus discloses a protein-based platform to which binding moieties are coupled thereto. Proteins are comprised of amino acid monomer units that are distinguished by their different side chains. Applicants assert that the carbon that gives rise to an appended side chain in a polypeptide is not a branching group wherein the number of branching groups pre-determines the number of attachment sites on the valency platform molecule (see also comments above regarding polypeptides). In proteins, even if the amino acid side chain is to be considered a branching group, there is no direct correlation between the number of branching groups and the valency (number of attachment sites for biologically active molecules), as not all amino acid side chains are available for binding. The number of attachment sites is therefore not a function of the number of branching groups on the platform, but rather is a function of the specific reactivity of each side chain, as only some of the branching groups give rise to attachment sites which are available for binding to a biologically active molecule.

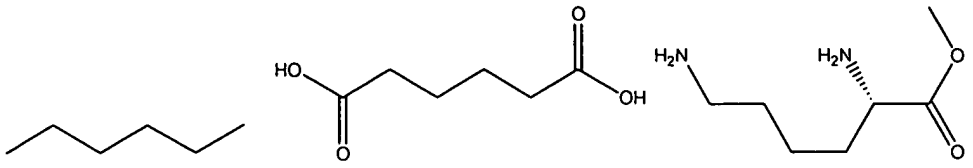
In contrast, the valency platform molecules claimed in the instant application require that the number of branching groups pre-determines the valency, or number of attachment sites for biologically active molecules. Hence, the number of branching groups establishes the number of attachment sites which in turn leads to a well-defined valency platform molecule. This feature is not taught or suggested by protein-based platforms. This rejection may be properly withdrawn.

Further, claim 22 has been amended to recite a single line of symmetry. As noted above, the peptide linkages in polypeptides, and subsequently in a protein, preclude the presence of a single line of symmetry.

The '116 patent, '979 patent, and '705 patent also disclose protein-based conjugates. The '116 patent discloses a method for treating a tumor using a radiotherapeutic immunoconjugate comprising a tumor specific monoclonal antibody or fragment thereof and an Auger electron emitting radionuclide, wherein the monoclonal antibody is capable of tumor cell nucleus localization. The '979 patent discloses methods for producing immunoconjugates, using a derivatized toxin protein in combination with an antibody under reaction conditions such that at least one native disulfide bond is reduced to form a thiol. The '705 patent discloses pharmaceutical compositions of ricin toxin A immunoconjugates comprising monoclonal antibodies and the cytotoxic ricin toxin A chain (column 3, lines 27-37). The protein-based conjugates of the cited references do not teach or suggest the compositions of the instant claims that require a valency platform molecule wherein the valency is predetermined by number of branching groups (see above discussion). Further, the protein-based conjugates of the cited references do not teach the compositions of amended claim 22, wherein the valency platform molecule has a single line of symmetry.

Further comments made by the Examiner in this section of the Office Action are addressed below.

The Examiner states that the Applicants have argued that applying the term "predetermined" to a structure of an organic compound somehow limits or changes its structure. The Examiner states several examples of organic compounds, including n-hexane, adipic acid, and lysine methyl ester, which are used in conjunction with the Examiner's argument that "no matter what the structure of a compound is, and how many branch points there are, the valency of the compound is determined (at least in part) by the number of branch points". These compounds, together with the Examiner's interpretation of the number of branching groups, valency and number of attachments sites, are reproduced below:



n-hexane
branching groups = 0
valency = 0
# of attachment sites = 0

adipic acid
branching groups = 0
valency = 2
# of attachment sites = 2

lysine methyl ester
branching groups = 1
valency = 2
# of attachment sites = 2

However, the language of the claim in question is: "wherein the valency of said platform molecule is predetermined by the number of branching groups." Applicants assert that the valency of the above molecules is a consequence of chemical reactivity, and not the number of branching groups. For instance, adipic acid and n-hexane do not comprise branching groups, yet adipic acid has 2 attachment sites while n-hexane has none. The number of branching groups in this instance does not determine in advance (*i.e.*, predetermine) the number of attachment sites, as there are no branching groups to give rise to attachment sites. The presence of attachment sites on adipic acid is not due to a positive correlation between branching groups (as there are none), but rather, it is a consequence of the particular chemical moieties on the molecule itself. Likewise, the absence of attachment sites on n-hexane is not due to the lack of branching groups, but rather is a consequence of the hydrocarbon moieties from which it is comprised.

The valency platform molecules of the present invention are produced such that they comprise branching groups, which in turn give rise to attachment sites for biologically active molecules. An attachment site is not present on the valency platform molecule without the presence of a branching group.

The Examiner also asserts that a valency of three may be obtained for a conjugate such as conjugate 20-II in Figure 6B. However, the well-established meaning of the term "valency" in the chemical arts is the overall combining capacity, which is independent of the actual occupancy. The valency, or overall combining capacity, is equivalent to the number of attachment sites, and is independent of the actual occupancy of the attachment sites by biologically active molecules.

The Examiner also comments on the term "attachment site" and notes that "one might infer, however, that applicants regard the term "attachment site" as meaning a functional group (on

the valency platform molecule) which will react readily with a functional group on the biologically active molecule". Applicants assert that indeed, an "attachment site" indicates a functional group on the valency platform molecule that will react with a functional group on the biologically active molecule. However, Applicants contend that this is not left for inference. For instance, the specification on page 3, lines 20-26 states, "In contrast to the above-described art, Applicants have developed conjugates comprising chemically-defined, non-polymeric valency platform molecules wherein the valency of the platform molecules is predetermined and wherein each attachment site is available for binding of a biological or chemical molecule." Page 17, lines 20-24 of the specification states that a "valency platform molecule" means a molecule " . . . containing sites which facilitate the attachment of a discreet number of biological and/or chemical molecules." It would therefore be clear to someone of skill in the art that an "attachment site" indicates a functional group on the valency platform molecule that will react with a functional group on the biologically active molecule.

In a related matter, the Examiner states that "there appears to be no discussion in the specification (pages 94-98) about how to attach the group designated "PN" to the phosphate monoester". However, Example 5, starting on page 94 of the specification depicts a schematic representation of the phosphoramidite type chemistry that may be used to link the "PN" to the valency platform molecule. Specifically, a thiol linker is utilized, wherein the thiol reacts with an attachment site on the valency platform molecule. Consider, for instance, Reaction Scheme 22 on the bottom of page 95. Therein, a phosphoramidite is treated under appropriate conditions to yield the Tr-5'-modified $(CA)_{10}$, whose disulfide bond is subsequently cleaved to provide a nucleophilic thiol moiety. This thiol, when treated with compound 20 (see page 34), reacts with the electrophilic attachment sites on the termini of the valency platform molecule to provide compound 20-I.

Applicants also refer the Examiner to pages 79 and 80 of the specification, which specifically state certain mutually reactive groups that may be utilized as attachment sites on the valency platform molecule and on the biologically active molecule to affect conjugation. Applicants contend that there are numerous places in the specification that state how to attach polynucleotides to the valency platform molecule. Further to the sections mentioned above, pages 20-26 discuss

numerous coupling strategies for conjugation of a polynucleotide to the valency platform molecules. Given the numerous examples and general strategies provided in the specification regarding this matter, the specification is not ambiguous as to attachment sites, or how to conjugate polynucleotides to the valency platform molecules.

Applicants respectfully request that this rejection be withdrawn.

U.S. Patent No. 4,289,872 and U.S. Patent No. 4,415,590

Claims 22-25, 33, 35, 37, 62 are rejected under 35 U.S.C. §103 as allegedly unpatentable over Denkewalter in U.S. Patent No. 4,289,872 ("the '872 patent") in view of Gerzon in U.S. Patent No. 4,415,590 ("the '590 patent"). Applicants respectfully traverse the rejection. The '872 patent discloses organic macromolecular compounds, such as polymeric lysine, to which other compounds may be linked via reactive substituent groups. The Examiner states that according to one interpretation, the external lysines would constitute the biologically active molecules, and at the same time, the lysines to which the external lysines are "conjugated" would provide the "attachment sites".

However, polylysine as a valency platform molecule does not teach or suggest the valency platform molecule of the conjugates recited in claim 22. The specific structural limitations such as branching groups that predetermine the valency are not taught or suggested by references disclosing polylysine. Applicants refer to the above discussion regarding polypeptides as platform molecules. This rejection may be properly withdrawn.

Applicants have further amended claim 22 to incorporate a single line of symmetry. Polylysine does not have a single line of symmetry due to the repeating peptide linkages and does not comprise branching groups wherein the number of branching groups pre-determines the number of attachment sites for biologically active molecules. Accordingly, the '872 patent does not teach or suggest the conjugates of claim 22.

The '590 patent discloses a mixture of L-lysine and L-glutamic acid in a therapeutic treatment of herpes and herpes-like infections. The disclosure in the '590 patent of lysine acting as a

biologically active molecule does not cure the deficiencies of the '872 patent. There is no further disclosure in the '590 patent that would render the instant claims obvious in view of the polylysine platforms disclosed in the '872 patent. The '872 patent, alone or together with the '590 patent does not teach or suggest the limitations recited in amended claim 22, and Applicants respectfully request withdrawal of the rejection.

U.S. Patent No. 4,349,538

Claims 22-24, 26, 29, 30, 58-60 are rejected under 35 U.S.C. §103 as allegedly unpatentable over Levy in U.S. Patent No. 4,349,538 ("the '538 patent"). Applicants respectfully traverse the rejection. Applicants address the '538 patent and the Examiner's comments in this section of the Office Action in turn below.

The '538 patent discloses a three component nuclease-resistant hydrophilic complex of polyriboinosinic-polyribocytidylic acid ("In.Cn"), poly-L-lysine, and carboxymethylcellulose. Applicants note that column 2, lines 46-50 state that "The carboxymethylcellulose, which is a hydrophilic material negatively charged at a neutral pH is an essential part of the complex, since without its presence, the In.Cn and the poly-l-lysine would form an intractable precipitate." Lines 51-58 of the same column state the order of addition of the components (poly-L-lysine, followed by carboxymethylcellulose, followed by In.Cn) as "critical to the preparation". It is clear that the teachings of the '538 patent are directed to a three component mixture, and further that a In.Cn-polylysine mixture would form an undesired precipitate.

Applicants note that three-component mixture disclosed in the '538 patent does not teach or suggest the chemically-defined conjugates as claimed. Applicants further refer to the above discussions regarding polylysine, and contend that polylysine does not teach the limitations recited in claim 22. Specifically, the valency of polylysine is not predetermined by the number of branching groups. This rejection may be properly withdrawn.

In addition, polylysine does not have a single line of symmetry as amended claim 22 recites.

The three component system of the '538 patent does not teach or suggest the claimed conjugates or the chemically defined valency platform molecules thereof. Polylysine does not teach or suggest a valency platform molecule wherein the valency is predetermined by the number of branching groups. In addition, the teachings of the '538 patent do not teach or suggest valency platform molecules having a single line of symmetry, as presently claimed. Applicants respectfully request withdrawal of the rejection.

Annals of the New York Academy of Sciences 475, 296-306, 1986
Borel in Journal of Immunological Methods 67 (2) 289-302, 1984

Claims 22-24, 26, 29, 30, 58-60, 63 are rejected under 35 U.S.C. §103 as allegedly unpatentable over Borel in Annals of the New York Academy of Sciences 475, 296-306, 1986 ("Borel '86") or Borel in Journal of Immunological Methods 67 (2) 289-302, 1984 ("Borel '84"). Applicants respectfully traverse the rejection. Borel '86 and Borel '84 both disclose conjugates of oligonucleotides with keyhole limpet hemocyamin (KLH) and with antibodies. Applicants refer to the above discussion of polypeptides. Specifically, Applicants note that the valency of polypeptides is not due to the number of branching groups (considering that an amino acid side chain is a branching group as suggested by the Examiner), but rather is a function of the specific chemical reactivity of *certain* amino acid side chains. The Examiner asserts that "the number of branching groups "predetermines" the valency of the valency platform molecule, or at least, the number of branching groups "predetermines" the maximum valency that is attainable. It may be the case that fully 100% of the lysines do not react with the aldehyde group." It is therefore clear that the Examiner is only considering lysine as a branching group and is ignoring amino acid side chains that do not react with the biologically active molecule. Applicants also note that the Examiner is interchanging "valency" with "occupancy" and respectfully note that the term valency refers to the overall combining capacity and is independent of actual occupancy. However, if the Examiner is to consider the side chain of a lysine amino acid monomer a branching group, then each and every amino acid side chain, whether it be the hydrocarbon of leucine, the aromatic functionality of phenylalanine or the acidic moiety of glutamate, must also be considered a branching group. Clearly, not all of these side chains are available as attachment sites for biologically active

molecules. Accordingly, a polypeptide does not have branching groups wherein the *number* of branching groups predetermines the valency, or number of attachment sites for biologically active molecules. This rejection may be properly withdrawn.

In addition, Applicants note that claim 22 has been amended to recite a single line of symmetry. The repeating amide linkage of polypeptides precludes these compounds from having a single line of symmetry, as recited in amended claim 22. The structural limitations recited in claim 22 are not taught or suggested by Borel '86 or Borel '84.

Applicants respectfully request withdrawal of the rejection.

Gene 72, 323-332, 1989

Claims 22-24, 26, 29, 30, 58-60, 63 are rejected under 35 U.S.C. §103 as allegedly unpatentable over Leonetti in Gene 72, 323-332, 1989 ("Leonetti"). Applicants respectfully traverse the rejection. Leonetti discloses conjugates of oligonucleotides and polylysine. Applicants refer to the above discussion of both polylysine and oligonucleotides as valency platform molecules. If polylysine were to be considered the valency platform molecule, as suggested by the Examiner, Applicants note that polylysine does not have a valency that is predetermined by the number of branching groups. This rejection may be properly withdrawn.

Applicants note that claim 22 has been amended to incorporate a single line of symmetry. Further, polylysine does not have a single line of symmetry as claimed in amended claim 22. Similarly, if the oligonucleotide were to be considered the valency platform molecule, Applicants note that it does not have a valency predetermined by the number of branching groups or a single line of symmetry. Accordingly, Leonetti does not teach or suggest the conjugates of the present invention and Applicants request withdrawal of the rejection.

CONCLUSION

In view of the above amendments and remarks, the Applicants submit that the pending claims are in condition for allowance, and such action is respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 252312005704. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated:

Respectfully submitted,

By _____

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